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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,521	03/19/2001	Caroline Kreutzer	P 278416 980183 BT-CIP	6186

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/810,521	KREUTZER ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this c mmunication appears n the c ver sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-18 and 21-32* is/are pending in the application.

4a) Of the above claim(s) *5-15,17,18,21 and 24-26* is/are withdrawn from consideration.

5)☒ Claim(s) *16* is/are allowed.

6)☒ Claim(s) *1,3 and 27-32* is/are rejected.

7)☒ Claim(s) *22 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/353,608* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1, 3, 5-18, and 21-32 are pending in the application.

Cancellation of claims 2, 4, 19, and 20, amendment to claims 1, 3, 22, and 23, and addition of claims 27-32 in Paper No. 15, filed 09/13/02, is acknowledged.

Claims 1, 3, 16, 22, 23, and 27-32 are being examined on the merits.

Claims 5-15, 17, 18, 21, and 24-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Receipt of a Declaration of Biological Deposit in Paper No. 16, filed 10/15/02, is acknowledged.

Receipt of Terminal Disclaimer in Paper No. 17, filed 10/15/02, is acknowledged.

Applicants' arguments filed in Paper No. 15 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

1. Claims 1, 3, 27, 28, and 30-32 are objected to in the recitation of "over-expressed" in claims 1, 3, 28, and 30-32 and "overexpressed" in claim 27. It is suggested that applicants maintain consistency of terms used in the claims by, for example, replacing "overexpressed" in claim 27 with "over-expressed".

2. Claims 22 and 23 are objected to because of the recitation of "SEQ ID No:". Applicants should identify the nucleic acid sequences using the proper sequence identifier "SEQ ID NO:". See 37 CFR 1.821 part (d) and MPEP 2422 regarding nucleotide sequence disclosure in a patent application. Appropriate correction is required.

3. Claim 30 is objected to in the recitation of "lyseE". This appears to be an incorrect spelling of "lysE" and the claim has been examined accordingly. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Rejection of claim 3 as being indefinite in the recitation of "the lysE gene", is maintained. There is insufficient antecedent basis for this limitation in the claim. The rejection was fully explained in a previous Office action. Applicants argue (page 4 of Paper No. 15) the claims have been amended to overcome the rejection. Applicants' argument is not found persuasive. There remains a lack of antecedent basis for the term described above. As such, the rejection is maintained for the reasons of record.

5. The term "over-expressed" in claims 1 (claim 4 dependent therefrom), 3, 28, and 30-32 and "overexpressed" in claim 27 is unclear absent a statement defining to what the overexpression of the recited genes is being compared. The terms "over-expressed" and "overexpressed" are relative terms and the claims should define and clearly state as to what the overexpression is being compared (i.e., overexpression in comparison to what level of expression?). This rejection is necessitated by amendment.

6. Claim 28 recites the limitation "said over-expressed aspartate kinase" in claim 27. Claim 27 recites "an overexpressed lysC gene" and not "an overexpressed aspartate kinase". As such, there is insufficient antecedent basis for this limitation in the claim. This rejection is necessitated by amendment.

7. Claim 29 recites the limitation "the aecD... ...gene". There is insufficient antecedent basis for this limitation in the claim. This rejection is necessitated by amendment.

8. Claim 29 is confusing in the recitation of "said dapA gene... ...is comprised in the aecD... ...gene". Based on the wording of the claim, particularly the phrase "comprised in the aecD... ...gene", the examiner has interpreted the meaning of the claim as the dapA gene is inserted into the aecD gene. However, based on Examples 16 and 17 of the instant specification (pages 31-33), it appears that applicants intended meaning of the claim to be an aecD gene linked to the recited dapA gene. It is suggested that applicants clarify the meaning of the claim. This rejection is necessitated by amendment.

Claim Rejections - 35 USC § 112, First Paragraph

9. The written description rejection of claims 1, 3, 27, 28, and 30-32 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons described below. The rejection as it applied to original claims 1-4 was fully explained in a previous Office action.

Claims 1, 3, 27, and 29 are drawn to L-lysine-producing Corynebacterium glutamicum bacteria comprising a genus of over-expressed C. glutamicum pyc genes and a genus of overexpressed C. glutamicum dapA genes wherein overexpression of said dapA gene is achieved using a genus of dapA promoters comprising the MC20 mutation of SEQ ID NO:5 or the MA20 mutation of SEQ ID NO:6 (claim 1) and optionally wherein a genus of C. glutamicum lysE genes are overexpressed (claim 3), a genus of C. glutamicum lysC genes encoding aspartate kinase (claim 27) or aspartate kinase that is resistant to lysine and/or threonine (claim 28) is overexpressed. Claims 30-32 are drawn to L-lysine producing Corynebacterium glutamicum bacteria comprising a genus of over-expressed C. glutamicum pyc genes, a genus of overexpressed C. glutamicum dapA genes, and a genus of overexpressed C. glutamicum lysE genes (claim 30), and optionally further comprising a C. glutamicum lysC gene encoding aspartate kinase (claim 31) or aspartate kinase that is resistant to lysine and/or threonine (claim 32) is overexpressed. Applicants argue the claims have been amended to limit the recited genes to those of C. glutamicum. Applicants' argument is not found persuasive. It is noted that the structures of C. glutamicum pyc, lysC, and lysE genes are well-known in the prior art. However, the specification fails to adequately describe the structures of a genus of C. glutamicum pyc, lysC, or lysE genes that are overexpressed and a genus of C. glutamicum lysC genes overexpressing an aspartate kinase that is resistant to feedback inhibition by lysine and/or threonine. Regarding overexpression of the pyc, lysC, and lysE genes, the specification discloses at page 7 that overexpression of a gene may be achieved by mutating the promoter and regulatory region or the ribosome binding site located upstream from the structural gene. Such structures of a genus of C. glutamicum pyc, lysC, and lysE overexpressing genes having mutations of the promoter, regulatory region, or ribosome binding site have not been disclosed in the specification. Furthermore, the

structures of a genus of lysC genes resulting in a feedback resistant aspartate kinase have not been disclosed in the specification. Such structures are an essential feature of the claimed invention and should therefore be adequately described in the specification. In the instant case, the genes have only been described by their function. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that:

> "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus".

Similarly with the claimed genus of genes, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the species within the genus from other genes such that one can visualize or recognize the identity of the members of the genus. The specification provides only two representative species of the claimed L-lysine-producing bacteria, i.e., C. glutamicum deposit numbers DSM12867 and DSM12868. Given the lack of description of representative species encompassed by the genera of genes recited in the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

10. The scope of enablement rejection of claims 1, 3, 27, 28, and 30-32 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons described below. The rejection as it applied to original claims 1-4was fully explained in a previous Office action. Applicants argue the claims have been amended to limit the recited genes to those of C. glutamicum. Applicants' argument is not found persuasive.

The specification, while being enabling for C. glutamicum deposit numbers DSM12867 and DSM12868, does not reasonably provide enablement for L-lysine-producing C. glutamicum bacteria comprising all C. glutamicum pyc genes overexpressed by any method and a C. glutamicum dapA gene wherein overexpression of said dapA gene is achieved using a dapA promoter comprising the MC20

mutation of SEQ ID NO:5 or the MA20 mutation of SEQ ID NO:6 (claim 1) and optionally wherein any C. glutamicum lysE gene is overexpressed by any method (claim 3), any C. glutamicum lysC gene encoding aspartate kinase (claim 27) or aspartate kinase that is resistant to lysine and/or threonine (claim 28) is overexpressed by any method. Claims 30-32 are drawn to L-lysine-producing Corynebacterium glutamicum bacteria comprising any C. glutamicum pyc gene overexpressed by any method, any C. glutamicum dapA gene overexpressed by any method, and any C. glutamicum lysE gene overexpressed by any method (claim 30), and optionally further comprising any C. glutamicum lysC gene encoding aspartate kinase (claim 31) or aspartate kinase that is resistant to lysine and/or threonine (claim 32) overexpressed by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Undue experimentation would be required to make the invention as broadly claimed. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). Applicants have provided an enabling disclosure only for the L-lysine-producing C. glutamicum having deposit numbers DSM12867 and DSM12868. It is noted that applicants disclose in the specification at page 7 that overexpression of a gene may be achieved by mutating a promoter, regulatory region, or ribosomal binding site of a gene. Applicants have not disclosed the alteration(s) to a pyc, lysE, or lysC gene resulting in overexpression of said genes or, in the case of lysC, feedback resistance of said encoded aspartate kinase. Without such guidance, one of skill in the art would be required to analyze each gene's promoter, regulatory regions, and ribosomal binding sites (if known in the art or identify said promoter, regulatory regions, and ribosomal binding sites if not known) for nucleotides that may be altered in order to obtain overexpression. In the case of lysC, one must further determine nucleotides that may be substituted to obtain an encoded aspartate kinase having feedback

resistance to lysine and/or threonine. Based on the guidance provided in the specification, it is highly unpredictable as to which of the nucleotides of a recited gene may be altered with an expectation of obtaining C. glutamicum bacteria overexpressing the recited genes or, in the case of lysC, overexpressing a feedback resistant aspartate kinase. As such, one of skill in the art would recognize that a large quantity of experimentation is necessary to make the broad scope of claimed L-lysine-producing C. glutamicum bacteria.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

11. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peters-Wendisch et al. (IDS reference OR; DE 19831609, published 04/15/1999, hereafter referred to as "Peters-Windisch") in view of Cremer et al. (IDS reference QR; EP 0435132, published 07/03/91, hereafter referred to as "Cremer"), Vrljic et al. (IDS reference PR; DE 19548222, published 06/26/97, hereafter referred to as "Vrlijic"), and Araki et al. (IDS reference RR; EP 0854189, published 07/22/1998, hereafter referred to as "Araki"). Claim 30 is drawn to L-lysine-producing C. glutamicum bacteria comprising overexpressed C. glutamicum pyc, dapA, and lysE genes. Claim 31 is drawn to the L-lysine-producing bacteria of claim 30 further comprising an overexpressed C. glutamicum lysC gene. This rejection is necessitated by amendment.

Peters-Wendisch teaches cloning of a C. glutamicum pyc gene by PCR (pages 3 and 4). The isolated C. glutamicum pyc gene was inserted into an expression vector for overexpression of the gene in C. glutamicum (pages 4 and 5). Peters-Wendisch teaches overexpression of a C. glutamicum pyc gene

significantly increased the yield of L-lysine in the culture medium (pages 5 and 6). Peters-Windisch does not teach co-expression of their pyc gene with a C. glutamicum dapA, lysC, or lysE gene.

Cremer teaches cloning of C. glutamicum dapA and lysC genes (page 4). The isolated genes were inserted into expression vectors for overexpression in C. glutamicum (page 5). Cremer teaches co-overexpression of dapA and lysC genes in C. glutamicum results in increased production of L-lysine relative to overexpression of dapA or lysC alone (pages 5-7).

Vrljic teaches cloning of a C. glutamicum lysE gene whose protein product is reportedly involved in lysine export (pages 4, 5, and Figure 1). Vrlijic teaches the results of overexpression of a C. glutamicum lysE gene are increased yields of L-lysine in the culture medium due to increased export of intracellular L-lysine into the culture medium (Figures 3 and 4).

Simultaneous overexpression of genes involved in a particular amino acid biosynthesis pathway or genes that increase production of a particular amino acid are well-known to one of ordinary skill in the art. Araki teaches that overexpression of a C. glutamicum dapA, lysC, dapB, lysA, or aspC gene alone in a C. glutamicum host cell resulted in only minor increases in L-lysine yields relative to wild-type C. glutamcium (page 18). Araki teaches co-overexpression of dapA, lysC, dapB, lysA, and aspC genes increased L-lysine yields by approximately 19 grams/L relative to wild-type C. glutamicum after 72 hours of cell growth (page 18).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Peters-Wendisch, Cremer, and Vrljic for a C. glutamicum transformed with expression vectors for co-overexpression of C. glutamicum pyc, dapA, lysC, and lysE genes as C. glutamicum co-transformed with expression vectors for co-overexpression of a plurality of genes for increased yields of an amino acid are well-known in the art as demonstrated by Cremer and Araki. One would have been motivated for a C. glutamicum transformed with expression vectors for co-overexpression of C. glutamicum pyc, dapA, lysC, and lysE genes in order to increase the yield of L-lysine. One would have a reasonable expectation of success for a C. glutamicum transformed with expression vectors for co-overexpression of C. glutamicum pyc, dapA, lysC, and lysE genes because of the results of Peters-Wendisch who teaches the cloning and

overexpression of pyc with increased L-lysine yields, Cremer who teaches synergistic increases in L-lysine production due to co-overexpression of dapA and lysC genes, and Vrljic who teaches increased L-lysine accumulation in the culture medium due to overexpression of lysE, and Araki who demonstrated co-overexpression of genes in C. glutamicum that, when expressed singly, result in only minor increases in L-lysine yields. Therefore, claims 30 and 31, drawn to L-lysine-producing C. glutamicum bacteria as described above would have been obvious to one of ordinary skill in the art.

Applicants argue the cited references do not teach or suggest overexpression of the recited genes via use of a dapA promoter comprising a MC20 mutation of SEQ ID NO:5 or the MA20 mutation of SEQ ID NO:6. Applicants' argument is not found persuasive. It is noted that neither claim 30 nor 31 recites the limitation of a dapA promoter comprising a MC20 mutation of SEQ ID NO:5 or the MA20 mutation of SEQ ID NO:6. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As demonstrated above, the cited references teach all claim limitations, there is motivation to combine the cited references, and a reasonable expectation of success exists for making the claimed invention based on the teachings provided in the cited references. As such, all three criteria to establish a *prima facie* case of obviousness have been satisfied.

Conclusion

12. Claims 1, 3, and 27-32 are rejected.

13. Claims 22 and 23 are objected to.

14. Claim 16 is in condition for allowance.

15. Claims 1, 3, 22, 23, and 27-29 would be allowable if rewritten to overcome the objection(s) and/or rejection(s) under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to

the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600